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S #	Comment	Database	Query String	Delete?
S4954		USPT	(5504005[pn] or 4460575[pn]) and tuberculosis	☐
S4953		USPT	(5504005[pn] or 4460575[pn]) and (32kd or (32 adj kd))	☐
S4952		USPT	5504005[pn] or 4460575[pn]	☐
S4951		USPT	554005[pn] or 4460575[pn]	☐
S4950		USPT	4789658[pn] or 5417970[pn]	☐
S4949		USPT	5916558[pn]	☐
S4948		USPT	5330754[pn]	☐
S4947		USPT	((vaccin$5 and (MF59 or (mf-59)))and @ad<19931123) or ((vaccin$5 and (MF59 or (mf-59)))and @prad<19931123)	☐
S4946		USPT	(vaccin$5 and (MF59 or (mf-59))) and @prad<19931123	☐
S4945		USPT	(vaccin$5 and (MF59 or (mf-59))) and @ad<19931123	☐
S4944		USPT	vaccin$5 and (MF59 or (mf-59))	☐
S4943		USPT	((tuberculosis same vaccin$5)and mf59) and @ad<19931123	☐
S4942		USPT	(tuberculosis same vaccin$5) and mf59	☐
S4941		USPT	(5108745[pn]) and ((mf-59) or mf59)	☐
S4940		USPT	5108745[pn]	☐

S4939		USPT	(vaccin$5 same (adjuvant with (Il2 or (il-2) or il12 or (il-12)))) and @prad<19931123	☐
S4938		USPT	(vaccin$5 same (adjuvant with (Il2 or (il-2) or il12 or (il-12)))) and @ad<19931123	☐
S4937		USPT	vaccin$5 same (adjuvant with (Il2 or (il-2) or il12 or (il-12)))	☐
S4936		USPT	((cultur$3 with (low adj temperature))and tuberculosis) and (adjuvant with (Il2 or (il-2) or il12 or (il-12)))	☐
S4935		USPT	BCG adj vaccin$5	☐
S4934		USPT	(cultur$3 with (low adj temperature)) and tuberculosis	☐
S4933		USPT	cultur$3 with (low adj temperature)	☐
S4932		USPT	(tuberculosis with (recombinant or transform$2)) and (low temperature)	☐
S4931		USPT	(tuberculosis with (recombinant or transform$2)) and ((28 adj degrees) or (28$1C))	☐
S4930		USPT	tuberculosis with (recombinant or transform$2)	☐
S4929		USPT	(((((85 or 85A) adj antigen$1)and @prad<19931123)or (((85 or 85A) adj antigen$1)and @ad<19931123))and ((smegmatis or vaccae)with (recombinant or transform$2))) and (smegmatis or vaccae)	☐
S4928		USPT	((((85 or 85A) adj antigen$1)and @prad<19931123)or (((85 or 85A) adj antigen$1)and @ad<19931123)) and ((smegmatis or vaccae)with (recombinant or transform$2))	☐
S4927		USPT	(((85 or 85A) adj antigen$1)and @prad<19931123) or (((85 or 85A) adj antigen$1)and @ad<19931123)	☐
S4926		USPT	((85 or 85A) adj antigen$1) and @ad<19931123	☐
S4925		USPT	((85 or 85A) adj antigen$1) and @prad<19931123	☐
S4924		USPT	(85 or 85A) adj antigen$1	☐

S4923		USPT	((smegmatis or vaccae)with (recombinant or transform$2)) and ((27 adj degrees) or (27$1C))	☐
S4922		USPT	((smegmatis or vaccae)with (recombinant or transform$2)) and ((28 adj degrees) or (28$1C))	☐
S4921		USPT	((smegmatis or vaccae)with (recombinant or transform$2)) and 28	☐
S4920		USPT	(smegmatis or vaccae) same degree$1	☐
S4919		USPT	((smegmatis or vaccae)with (recombinant or transform$2)) same degree$1	☐
S4918		USPT	(smegmatis or vaccae) and (28$1 adj degree$1)	☐
S4917		USPT	((((smegmatis or vaccae)with (recombinant or transform$2))and (tuberculosis same vaccin$5))and @ad<19931123) or ((((smegmatis or vaccae)with (recombinant or transform$2))and (tuberculosis same vaccin$5))and @prad<19931123)	☐
S4916		USPT	(((smegmatis or vaccae)with (recombinant or transform$2))and (tuberculosis same vaccin$5)) and @prad<19931123	☐
S4915		USPT	(((smegmatis or vaccae)with (recombinant or transform$2))and (tuberculosis same vaccin$5)) and @ad<19931123	☐
S4914		USPT	((smegmatis or vaccae)with (recombinant or transform$2)) and (tuberculosis same vaccin$5)	☐
S4913		USPT	(smegmatis or vaccae) with (recombinant or transform$2)	☐
S4912		USPT	smegmatis or vaccae	☐
S4911		USPT	tuberculosis same vaccin$5	☐
S4910		USPT	6159702[pn]	☐
S4909		USPT	(((combination therap$3))and (autoimmune disease)) and @ad<19950307	☐
S4908		USPT	((combination therap$3)) and (autoimmune disease)	☐
S4907		USPT	((pharmacuetical composition$1)) [ab]	☐

S4906		USPT	(tissue rejection) same ((combination therap$3))	☐
S4905		USPT	(autoimmune disease) same ((combination therap$3))	☐

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S #	Comment	Database	Query String	Delete?
S4704		USPT	PTI	☐
S4703		USPT	(spi6 or (spi-6)) and @ad<19990312	☐
S4702		USPT	spi6 or (spi-6)	☐
S4701		USPT	serpinB6 or serpin6B or (serpinB-6) or (serpin6-B) or (serpin-B6) or (serpin-6B) or (serpin adj2 6)	☐
S4700		USPT	((((((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @ad<19990312)or (((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @prad<19990312))and (cancer$1 or tumor$1 or tumour$1 or neoplas$3 or malignan$4))with (cytoplasm$2 or intracellular$2 or (intra-cellular$2))) and @prad<19990312	☐
S4699		USPT	((((((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @ad<19990312)or (((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @prad<19990312))and (cancer$1 or tumor$1 or tumour$1 or neoplas$3 or malignan$4))with (cytoplasm$2 or intracellular$2 or (intra-cellular$2))) and @ad<19990312	☐
S4698		USPT	(antiproteinase or antiprotease or (anti-protienase) or (anti-protease)) with (cytoplasm$2 or intracellular$2 or (intra-cellular$2))	☐

S4697		USPT	(antiproteinase or antiprotease or (anti-protienase) or (anti-protease)) with (cytoplasm$2 or intracellular$2)	☐
S4696		USPT	antiproteinase or antiprotease or (anti-protienase) or (anti-protease)	☐
S4695		USPT	(((((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @ad<19990312)or (((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @prad<19990312))and (cancer$1 or tumor$1 or tumour$1 or neoplas$3 or malignan$4)) and ((ovalbumin with (proteinase adj inhibitor$1)) or (ov-serpin$1))	☐
S4694		USPT	((((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @ad<19990312)or (((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @prad<19990312)) and (cancer$1 or tumor$1 or tumour$1 or neoplas$3 or malignan$4)	☐
S4693		USPT	(((cap-1)and @ad<19990312)or ((cap-1)and @prad<19990312)) and (placenta$1 or serpin$1)	☐
S4692		USPT	((cap-1)and @ad<19990312) or ((cap-1)and @prad<19990312)	☐
S4691		USPT	(cap-1) and @prad<19990312	☐
S4690		USPT	(cap-1) and @ad<19990312	☐
S4689		USPT	cap-1	☐
S4688		USPT	(((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @ad<19990312) or (((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1))and @prad<19990312)	☐
S4687		USPT	((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1)) and @prad<19990312	☐
S4686		USPT	((ovalbumin with (proteinase adj inhibitor$1))or (ov-serpin$1)) and @ad<19990312	☐
S4685		USPT	(ovalbumin with (proteinase adj inhibitor$1)) or (ov-serpin$1)	☐

S4684		USPT	ov-serpin$1	☐
S4683		USPT	ovalbumin with (proteinase adj inhibitor$1)	☐
S4682		USPT	proteinase adj inhibitor$1	☐
S4681		USPT	placental adj (plasmin or thrombin or trypsin) adj inhibitor	☐
S4680		USPT	((23 adj (kd or kda or kdalton$1))or (23 adj (kd or kda or kdalton$1))) not ((23 adj (kd or kda or kdalton$1))or (23 adj (kd or kda or kdalton$1)))	☐
S4679		USPT	((24 adj (kd or kda or kdalton$1))and @ad<19931123) or ((24 adj (kd or kda or kdalton$1))and @prad<19931123)	☐
S4678		USPT	((tuberculosis)same (extracellular or secreted)) and @prad<19931123	☐
S4677		USPT	((tuberculosis)same (extracellular or secreted)) and @ad<19931123	☐
S4676		USPT	((24 adj (kd or kda or kdalton$1))same (antigen$1)) and @ad<19931123	☐
S4675		USPT	((24 adj (kd or kda or kdalton$1))and @prad<19931123) or ((24 adj (kd or kda or kdalton$1))and @ad<19931123)	☐
S4674		USPT	((24 adj (kd or kda or kdalton$1))same (antigen$1)) and @prad<19931123	☐
S4673		USPT	((24 adj (kd or kda or kdalton$1))same (antigen$1)) and @ad<19931123	☐
S4672		USPT	((tuberculosis)same (extracellular or secreted)) same (antigen$1)	☐
S4671		USPT	(tuberculosis) same (extracellular or secreted)	☐
S4670		USPT	(110kd or 110k or 110kda or 110kdalton$1) with (80kd or 80k or 80kda or 80kdalton$1) with (71kd or 71k or 71kda or 71kdalton$1) with (58kd or 58k or 58kda or 58kdalton$1) with (45kd or 45k or 45kda or 45kdalton$1) with (32kd or 32k or 32kda or 32kdalton$1)	☐
S4669		USPT	32kd or 32k or 32kda or 32kdalton$1	☐
S4668		USPT	45kd or 45k or 45kda or 45kdalton$1	☐

S4667		USPT	58kd or 58k or 58kda or 58kdalton$1	☐
S4666		USPT	71kd or 71k or 71kda or 71kdalton$1	☐
S4665		USPT	80kd or 80k or 80kda or 80kdalton$1	☐
S4664		USPT	110kd or 110k or 110kda or 110kdalton$1	☐
S4663		USPT	110kd or 110kda or 110kdalton$1	☐
S4662		USPT	110kd or kda or 110kdalton$1	☐
S4661		USPT	(110 adj (kd or kda or kdalton$1)) same (80 adj (kd or kda or kdalton$1)) same (71 adj (kd or kda or kdalton$1)) same (58 adj (kd or kda or kdalton$1)) same (45 adj (kd or kda or kdalton$1)) same (32 adj (kd or kda or kdalton$1)) same (30 adj (kd or kda or kdalton$1)) same (24 adj (kd or kda or kdalton$1)) same (23 adj (kd or kda or kdalton$1)) same (16 adj (kd or kda or kdalton$1)) same (14 adj (kd or kda or kdalton$1)) same (12 adj (kd or kda or kdalton$1))	☐
S4660		USPT	12 adj (kd or kda or kdalton$1)	☐
S4659		USPT	14 adj (kd or kda or kdalton$1)	☐
S4658		USPT	16 adj (kd or kda or kdalton$1)	☐
S4657		USPT	23 adj (kd or kda or kdalton$1)	☐
S4656		USPT	24 adj (kd or kda or kdalton$1)	☐
S4655		USPT	30 adj (kd or kda or kdalton$1)	☐

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S #	Comment	Database	Query String	Delete?
S4654		USPT	32 adj (kd or kda or kdalton$1)	☐
S4653		USPT	45 adj (kd or kda or kdalton$1)	☐
S4652		USPT	58 adj (kd or kda or kdalton$1)	☐
S4651		USPT	71 adj (kd or kda or kdalton$1)	☐
S4650		USPT	80 adj (kd or kda or kdalton$1)	☐
S4649		USPT	110 adj (kd or kda or kdalton$1)	☐
S4648		USPT	(((tuberculosis)and (58 or 58kd or 58kda or 58kdalton$1))and @prad<19931123) or (((tuberculosis)and (58 or 58kd or 58kda or 58kdalton$1))and @ad<19931123)	☐
S4647		USPT	((tuberculosis)and (110 same 80 same 71 same 58 same 45 same 32 same 32 same 30 same 24 same 23 same 16 same 14 same 12)) and @prad<19931123	☐
S4646		USPT	((tuberculosis)and (110 same 80 same 71 same 58 same 45 same 32 same 32 same 30 same 24 same 23 same 16 same 14 same 12)) and @ad<19931123	☐
			(((tuberculosis)and (vaccine$1 or vaccination or vaccinating))and	

S4645		USPT	(secret$3 or extracellular$2)) and (110 same 80 same 71 same 58 same 45 same 32 same 32 same 30 same 24 same 23 same 16 same 14 same 12)	☐
S4644		USPT	(((tuberculosis)and (71 or 71kd or 80kda or 71kda or 71kdalton$1))and @prad<19931123) or (((tuberculosis)and (71 or 71kd or 80kda or 71kda or 71kdalton$1))and @ad<19931123)	☐
S4643		USPT	(((tuberculosis)and (110 or 110kd or 110kda or 110kdalton$1))and ((tuberculosis)and (80 or 80kd or 800kda or 80kdalton$1))and ((tuberculosis)and (71 or 71kd or 80kda or 71kda or 71kdalton$1))and ((tuberculosis)and (58 or 58kd or 58kda or 58kdalton$1))and ((tuberculosis)and (45 or 45kd or 45kda or 45kdalton$1))and ((tuberculosis)and (32 or 32kd or 32kda or 32kdalton$1))and ((tuberculosis)and (30 or 30kd or 30kda or 30kdalton$1))and ((tuberculosis)and (24 or 24kd or 24kda or 24kdalton$1))and ((tuberculosis)and (23 or 23kd or 23kda or 23kdalton$1))and ((tuberculosis)and (16 or 16kd or 16kda or 16kdalton$1))and ((tuberculosis)and (14 or 14kd or 14kda or 14kdalton$1))and ((tuberculosis)and (12 or 12kd or 12kda or 12kdalton$1))) and @ad<19931123	☐
			(((tuberculosis)and (110 or 110kd or 110kda or 110kdalton$1))and ((tuberculosis)and (80 or 80kd or 800kda or 80kdalton$1))and ((tuberculosis)and (71 or 71kd or 80kda or 71kda or 71kdalton$1))and ((tuberculosis)and (58 or 58kd or 58kda or 58kdalton$1))and ((tuberculosis)and (45 or 45kd or 45kda or 45kdalton$1))and ((tuberculosis)and (32 or	

S4642		USPT	32kd or 32kda or 32kdalton$1))and ((tuberculosis)and (30 or 30kd or 30kda or 30kdalton$1))and ((tuberculosis)and (24 or 24kd or 24kda or 24kdalton$1))and ((tuberculosis)and (23 or 23kd or 23kda or 23kdalton$1))and ((tuberculosis)and (16 or 16kd or 16kda or 16kdalton$1))and ((tuberculosis)and (14 or 14kd or 14kda or 14kdalton$1))and ((tuberculosis)and (12 or 12kd or 12kda or 12kdalton$1))) and @prad<19931123	☐
S4641		USPT	((tuberculosis)and (110 or 110kd or 110kda or 110kdalton$1)) and ((tuberculosis)and (80 or 80kd or 800kda or 80kdalton$1)) and ((tuberculosis)and (71 or 71kd or 80kda or 71kda or 71kdalton$1)) and ((tuberculosis)and (58 or 58kd or 58kda or 58kdalton$1)) and ((tuberculosis)and (45 or 45kd or 45kda or 45kdalton$1)) and ((tuberculosis)and (32 or 32kd or 32kda or 32kdalton$1)) and ((tuberculosis)and (30 or 30kd or 30kda or 30kdalton$1)) and ((tuberculosis)and (24 or 24kd or 24kda or 24kdalton$1)) and ((tuberculosis)and (23 or 23kd or 23kda or 23kdalton$1)) and ((tuberculosis)and (16 or 16kd or 16kda or 16kdalton$1)) and ((tuberculosis)and (14 or 14kd or 14kda or 14kdalton$1)) and ((tuberculosis)and (12 or 12kd or 12kda or 12kdalton$1))	☐
S4640		USPT	(((tuberculosis)and (30 or 30kd or 30kda or 30kdalton$1))and @prad<19931123) or (((tuberculosis)and (30 or 30kd or 30kda or 30kdalton$1))and @ad<19931123)	☐
S4639		USPT	(((tuberculosis)and (30 or 30kd or 30kda or 30kdalton$1))and (vaccine$1 or vaccination or vaccinating)) and @prad<19931123	☐

S4638		USPT	(((tuberculosis)and (30 or 30kd or 30kda or 30kdalton$1))and (vaccine$1 or vaccination or vaccinating)) and @ad<19931123	☐
S4637		USPT	((((tuberculosis)and (110 or 110kd or 110kda or 110kdalton$1))and ((tuberculosis)and (110 or 110kd or kda or 110kdalton$1))and ((tuberculosis)and (110 or 110kd or 110kda or 110kdalton$1))and ()and ()and ())and ((tuberculosis)and (45 or 45kd or 45kda or 45kdalton$1))and ((tuberculosis)and (32 or 32kd or 32kda or 32kdalton$1))and ((tuberculosis)and (30 or 30kd or 30kda or 30kdalton$1))and ((tuberculosis)and (24 or 24kd or 24kda or 24kdalton$1))and ((tuberculosis)and (23 or 23kd or 23kda or 23kdalton$1))and ((tuberculosis)and (16 or 16kd or 16kda or 16kdalton$1))and ((tuberculosis)and (14 or 14kd or 14kda or 14kdalton$1))and ((tuberculosis)and (12 or 12kd or 12kda or 12kdalton$1))) and (vaccine$1 or vaccination or vaccinating)	☐
S4636		USPT	(((tuberculosis)and (110 or 110kd or 110kda or 110kdalton$1))and ((tuberculosis)and (110 or 110kd or kda or 110kdalton$1))and ((tuberculosis)and (110 or 110kd or 110kda or 110kdalton$1))and ()and ()and ()) and ((tuberculosis)and (45 or 45kd or 45kda or 45kdalton$1)) and ((tuberculosis)and (32 or 32kd or 32kda or 32kdalton$1)) and ((tuberculosis)and (30 or 30kd or 30kda or 30kdalton$1)) and ((tuberculosis)and (24 or 24kd or 24kda or 24kdalton$1)) and ((tuberculosis)and (23 or 23kd or 23kda or 23kdalton$1)) and ((tuberculosis)and (16 or 16kd or 16kda or 16kdalton$1)) and ((tuberculosis)and (14 or 14kd or 14kda or 14kdalton$1)) and ((tuberculosis	☐

			)and (12 or 12kd or 12kda or 12kdalton$1))	
S4635		USPT	((tuberculosis)and (110 or 110kd or 110kda or 110kdalton$1)) and ((tuberculosis)and (110 or 110kd or kda or 110kdalton$1)) and ((tuberculosis)and (110 or 110kd or 110kda or 110kdalton$1)) and () and () and ()	☐
S4634		USPT	(tuberculosis) and (12 or 12kd or 12kda or 12kdalton$1)	☐
S4633		USPT	(tuberculosis) and (14 or 14kd or 14kda or 14kdalton$1)	☐
S4632		USPT	(tuberculosis) and (16 or 16kd or 16kda or 16kdalton$1)	☐
S4631		USPT	(tuberculosis) and (23 or 23kd or 23kda or 23kdalton$1)	☐
S4630		USPT	(tuberculosis) and (24 or 24kd or 24kda or 24kdalton$1)	☐
S4629		USPT	(tuberculosis) and (30 or 30kd or 30kda or 30kdalton$1)	☐
S4628		USPT	(tuberculosis) and (32 or 32kd or 32kda or 32kdalton$1)	☐
S4627		USPT	(tuberculosis) and (45 or 45kd or 45kda or 45kdalton$1)	☐
S4626		USPT	(tuberculosis) and (58 or 58kd or 58kda or 58kdalton$1)	☐
S4625		USPT	(tuberculosis) and (71 or 71kd or 80kda or 71kda or 71kdalton$1)	☐
S4624		USPT	(tuberculosis) and (80 or 80kd or 800kda or 80kdalton$1)	☐
S4623		USPT	(tuberculosis) and (110 or 110kd or 110kda or 110kdalton$1)	☐
S4622		USPT	(tuberculosis) and (110 or 110kd or kda or 110kdalton$1)	☐
S4621		USPT	(tuberculosis) and (110kd$1 or (110k adj d$1) or (110 adj kd$1))	☐
S4620		USPT	tuberculosis	☐

S4619		JPAB,EPAB,DWPI	((tuberculosis)and (vaccine$1 or vaccination or vaccinating)) and (secret$3 or extracellular$2)	☐
S4618		JPAB,EPAB,DWPI	(tuberculosis) and (vaccine$1 or vaccination or vaccinating)	☐
S4617		JPAB,EPAB,DWPI	tuberculosis	☐
S4616		JPAB,EPAB,DWPI	((mycobacterium or tuberculosis)and (vaccine$1 or vaccination or vaccinating)) and (secret$3 or extracellular$2)	☐
S4615		JPAB,EPAB,DWPI	(mycobacterium or tuberculosis) and (vaccine$1 or vaccination or vaccinating)	☐
S4614		JPAB,EPAB,DWPI	mycobacterium or tuberculosis	☐
S4613		USPT	((mycobacterium or tuberculosis)and (vaccine with (culture adj (medium or media or broth)))) and @prad<19931123	☐
S4612		USPT	((mycobacterium or tuberculosis)and (vaccine with (culture adj (medium or media or broth)))) and @ad<19931123	☐
S4611		USPT	((mycobacterium or tuberculosis)and (vaccine with (culture adj (medium or media or broth)))) not (((((mycobacterium or tuberculosis)with (vaccinating or vaccination or vaccine$1))and @ad<19931123)or (((mycobacterium or tuberculosis)with (vaccinating or vaccination or vaccine$1))and @prad<19931123))and (secret$3 or extracellular$2))	☐
S4610		USPT	(mycobacterium or tuberculosis) and (vaccine with (culture adj (medium or media or broth)))	☐
S4609		USPT	(mycobacterium or tuberculosis) same (vaccine with (culture adj (medium or media or broth)))	☐
S4608		USPT	vaccine with (culture adj (medium or media or broth))	☐
			((mycobacterium or tuberculosis	

S4607		USPT	)with (vaccinating or vaccination or vaccine$1)) same (culture adj (medium or media or broth))	☐
S4606		USPT	((((mycobacterium or tuberculosis)with (vaccinating or vaccination or vaccine$1))and @ad<19931123)or (((mycobacterium or tuberculosis)with (vaccinating or vaccination or vaccine$1))and @prad<19931123)) and (secret$3 or extracellular$2)	☐
S4605		USPT	(((mycobacterium or tuberculosis)with (vaccinating or vaccination or vaccine$1))and @ad<19931123) or (((mycobacterium or tuberculosis)with (vaccinating or vaccination or vaccine$1))and @prad<19931123)	☐

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S #	Comment	Database	Query String	Delete?
S4604		USPT	((mycobacterium or tuberculosis)with (vaccinating or vaccination or vaccine$1)) and @prad<19931123	☐
S4603		USPT	((mycobacterium or tuberculosis)with (vaccinating or vaccination or vaccine$1)) and @ad<19931123	☐
S4602		USPT	(((serpin$1)with (cytoplasm$2 or (non-secreted) or nonsecreted or intracellular$2 or (intra-cellular$2)))and @prad<19990312) and @prad<19931123	☐
S4601		USPT	(((serpin$1)with (cytoplasm$2 or (non-secreted) or nonsecreted or intracellular$2 or (intra-cellular$2)))and @prad<19990312) and @ad<19931123	☐
S4600		USPT	(mycobacterium or tuberculosis) with (vaccinating or vaccination or vaccine$1)	☐
S4599		USPT	(((mycobacterium or tuberculosis)with vaccin$6)and @ad<19931123) or (((mycobacterium or tuberculosis)with vaccin$6)and @prad<19931123)	☐

S4598		USPT	((mycobacterium or tuberculosis)with vaccin$6) and @prad<19931123	☐
S4597		USPT	((mycobacterium or tuberculosis)with vaccin$6) and @ad<19931123	☐
S4596		USPT	(mycobacterium or tuberculosis) with vaccin$6	☐
S4595		USPT	(mycobacterium or tuberculosis) with vaccin$5	☐
S4594		USPT	mycobacterium or tuberculosis	☐
S4593		USPT	(thrombin inhibitor) with placent$2	☐
S4592		USPT	thrombin inhibitor	☐
S4591		USPT	(((serpin$1)with (cytoplasm$2 or (non-secreted) or nonsecreted or intracellular$2 or (intra-cellular$2)))and @ad<19990312) or (((serpin$1)with (cytoplasm$2 or (non-secreted) or nonsecreted or intracellular$2 or (intra-cellular$2)))and @prad<19990312)	☐
S4590		USPT	((serpin$1)with (cytoplasm$2 or (non-secreted) or nonsecreted or intracellular$2 or (intra-cellular$2))) and @prad<19990312	☐
S4589		USPT	((serpin$1)with (cytoplasm$2 or (non-secreted) or nonsecreted or intracellular$2 or (intra-cellular$2))) and @ad<19990312	☐
S4588		USPT	(serpin$1) with (cytoplasm$2 or (non-secreted) or nonsecreted or intracellular$2 or (intra-cellular$2))	☐
S4587		USPT	serpin$1	☐
S4586		USPT	serpin$1	☐
			(((CAP)adj5 (cancer$1 or tumor$1 or tumour$1 or malignan$4 or	

S4585		USPT	neoplas$3))or ((CAP)adj5 (bladder or kidney or renal or breast or mammary or necro$3))) and ($proteinase or $protease)	☐
S4584		USPT	((CAP)adj5 (cancer$1 or tumor$1 or tumour$1 or malignan$4 or neoplas$3)) or ((CAP)adj5 (bladder or kidney or renal or breast or mammary or necro$3))	☐
S4583		USPT	(CAP) adj5 (bladder or kidney or renal or breast or mammary or necro$3)	☐
S4582		USPT	(CAP) adj5 (cancer$1 or tumor$1 or tumour$1 or malignan$4 or neoplas$3)	☐
S4581		USPT	(CAP) same kidney	☐
S4580		USPT	(((protease or proteinase) near inhibitor near (6 or six or VI))or (cytoplasm$2 adj2 (antiprotease or antiproteinase or (anti-protease) or (anti-proteinase)))) same kidney	☐
S4579		USPT	(placental near thrombin near inhibitor) same kidney	☐
S4578		USPT	(((PI-6) or (pi near 6) or pi6 or (PI-VI) or (PI near VI) or PIVI)or (((PI-6) or (pi near 6) or pi6)adj2 (6 or VI or six))) same kidney	☐
S4577		JPAB,EPAB,DWPI	(((protease or proteinase) near inhibitor near (6 or six or VI))or (cytoplasm$2 adj2 (antiprotease or antiproteinase or (anti-protease) or (anti-proteinase)))or ((PI-6) or (pi near 6) or pi6)) same kidney	☐
S4576		JPAB,EPAB,DWPI	((((PI-6) or (pi near 6) or pi6 or (PI-VI) or (PI near VI) or PIVI)same (bladder or kideny or renal or breast or mammary or necro$3))adj2 (6 or VI or six)) or ((PI-VI) or (PI near VI) or PIVI)	☐
S4575		JPAB,EPAB,DWPI	(((protease or proteinase) near inhibitor)) adj2 (6 or VI or six)	☐
S4574		JPAB,EPAB,DWPI	((protease or proteinase) near inhibitor)	☐

S4573		JPAB,EPAB,DWPI	(PI-VI) or (PI near VI) or PIVI	☐
S4572		USPT	(((PI-6) or (pi near 6) or pi6 or (PI-VI) or (PI near VI) or PIVI)same (bladder or kideny or renal or breast or mammary or necro$3)) or (((PI-6) or (pi near 6) or pi6 or (PI-VI) or (PI near VI) or PIVI)same (cancer$1 or tumor$1 or tumour$1 or malignan$4 or neoplas$3))	☐
S4571		USPT	(((PI-6) or (pi near 6) or pi6 or (PI-VI) or (PI near VI) or PIVI)or (((PI-6) or (pi near 6) or pi6)adj2 (6 or VI or six))) same (bladder or kideny or renal or breast or mammary or necro$3)	☐
S4570		USPT	(((PI-6) or (pi near 6) or pi6 or (PI-VI) or (PI near VI) or PIVI)or (((PI-6) or (pi near 6) or pi6)adj2 (6 or VI or six))) same (cancer$1 or tumor$1 or tumour$1 or malignan$4 or neoplas$3)	☐
S4569		USPT	((PI-6) or (pi near 6) or pi6 or (PI-VI) or (PI near VI) or PIVI) or (((PI-6) or (pi near 6) or pi6)adj2 (6 or VI or six))	☐
S4568		USPT	(((protease or proteinase) near inhibitor)) adj2 (6 or VI or six)	☐
S4567		USPT	((protease or proteinase) near inhibitor)	☐
S4566		USPT	(PI-6) or (pi near 6) or pi6 or (PI-VI) or (PI near VI) or PIVI	☐
S4565		JPAB,EPAB,DWPI	(((protease or proteinase) near inhibitor near (6 or six or VI))or (cytoplasm$2 adj2 (antiprotease or antiproteinase or (anti-protease) or (anti-proteinase)))or ((PI-6) or (pi near 6) or pi6)) and (bladder or kideny or renal or breast or mammary or necro$3)	☐
S4564		JPAB,EPAB,DWPI	(((protease or proteinase) near inhibitor near (6 or six or VI))or (cytoplasm$2 adj2 (antiprotease or antiproteinase or (anti-protease) or (anti-proteinase)))or ((PI-6) or (pi	☐

			near 6) or pi6)) and (cancer$1 or tumor$1 or tumour$1 or malignan$4 or neoplas$3)	
S4563		JPAB,EPAB,DWPI	((protease or proteinase) near inhibitor near (6 or six or VI)) or (cytoplasm$2 adj2 (antiprotease or antiproteinase or (anti-protease) or (anti-proteinase))) or ((PI-6) or (pi near 6) or pi6)	☐
S4562		JPAB,EPAB,DWPI	(PI-6) or (pi near 6) or pi6	☐
S4561		JPAB,EPAB,DWPI	placental near thrombin near inhibitor	☐
S4560		JPAB,EPAB,DWPI	cytoplasm$2 adj2 (antiprotease or antiproteinase or (anti-protease) or (anti-proteinase))	☐
S4559		JPAB,EPAB,DWPI	(protease or proteinase) near inhibitor near (6 or six or VI)	☐
S4558		USPT	(placental near thrombin near inhibitor) same (cancer$1 or tumor$1 or tumour$1 or malignan$4 or neoplas$3)	☐
S4557		USPT	(placental near thrombin near inhibitor) same (bladder or kideny or renal or breast or mammary or necro$3)	☐
S4556		USPT	(((protease or proteinase) near inhibitor near (6 or six or VI))or (cytoplasm$2 adj2 (antiprotease or antiproteinase or (anti-protease) or (anti-proteinase)))) same (bladder or kideny or renal or breast or mammary or necro$3)	☐
S4555		USPT	(((protease or proteinase) near inhibitor near (6 or six or VI))or (cytoplasm$2 adj2 (antiprotease or antiproteinase or (anti-protease) or (anti-proteinase)))) and (cancer$1 or tumor$1 or tumour$1 or malignan$4 or neoplas$3)	☐

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L3: Entry 1 of 2 File: USPT Apr 2, 1996

US-PAT-NO: 5504005
DOCUMENT-IDENTIFIER: US 5504005 A

TITLE: Recombinant mycobacterial vaccine

DATE-ISSUED: April 2, 1996

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APPL-NO: 7/ 361944
DATE FILED: June 5, 1989

PARENT-CASE:
DESCRIPTION 1. Related Applications This application is a continuation-in-part of application Ser. No. 07/223,089, filed Jul. 22, 1988, abandoned, entitled "Stable Expression of Cloned Genes in Mycobacteria Using Phage and Plasmid Vectors" and of application Ser. No. 07/216,390, filed Jul. 7, 1988, abandoned, entitled "Recombinant Mycobacteria Having DNA of Interest Stably Integrated Into Genomic DNA, which are contination-in-part applications of application Ser. No. 07/163,546, filed Mar. 3, 1988, abandoned, entitled "Recombinant Mycobacterial Vaccine", which is a continuation-in-part of application Ser. No. 07/020,451, filed Mar. 2, 1987, abandoned entitled "Recombinant Mycobacterial Vaccine." The teachings of these four related applications are incorporated herein by reference.

INT-CL: [6] C12N 15/64, C12N 15/66, C12N 15/74
US-CL-ISSUED: 435/253.1; 435/69.1, 435/69.3, 435/69.51, 435/69.52, 435/172.1, 435/172.3, 435/183, 435/189, 435/207, 435/252.33, 435/320.1
US-CL-CURRENT: 435/472; 435/183, 435/189, 435/207, 435/252.33, 435/253.1, 435/320.1, 435/69.1, 435/69.3, 435/69.51, 435/69.52
FIELD-OF-SEARCH: 435/69.1, 435/69.51, 435/69.3, 435/69.52, 435/71.1, 435/69.5, 435/71.2, 435/172.1, 435/172.3, 435/235, 435/252.33, 435/253.1, 435/183, 435/320, 935/22, 935/23, 935/24, 935/26, 935/27, 935/29, 935/31, 935/52, 935/55, 935/56, 935/58, 935/72

PRIOR-ART-DISCLOSED:

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0127153	December 1984	EPX	

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ART-UNIT: 184
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ASSISTANT-EXAMINER: LeGuyader; J.
ATTY-AGENT-FIRM: Hamilton, Brook, Smith & Reynolds

ABSTRACT:

Recombinant mycobacterial vaccine vehicles capable of expressing DNA of interest which encodes at least one protein antigen for at least one pathogen against which an immune response is desired and which can be incorporated into the mycobacteria or stably integrated into the mycobacterial genome. The vaccine vehicles are useful for administration to mammalian hosts for purposes of immunization. A recombinant vector which replicates in E. coli but not in mycobacteria is also disclosed. The recombinant vector includes 1) a mycobacterial gene or portions thereof, necessary for recombination with homologous sequences in the genome of mycobacteria transformed with the recombinant plasmid; 2) all or a portion of a gene which encodes a polypeptide or protein whose expression is desired in mycobacteria transformed with the recombinant plasmid; 3) DNA sequences necessary for replication and selection in E. coli; and 4) DNA sequences necessary for selection in mycobacteria (e.g., drug resistance). The present invention also relates to two types of recombinant vectors useful in introducing DNA of interest into mycobacteria, where it is expressed. One type of vector is a recombinant phasmid capable of replicating as a plasmid in E. coli and of lysogenizing a mycobacterial host. The other type of vector is a recombinant plasmid which can be introduced into mycobacteria, where it is stably maintained extrachromosomally.

29 Claims, 23 Drawing figures

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L7: Entry 6 of 6 File: USPT Apr 2, 1996

DOCUMENT-IDENTIFIER: US 5504005 A
TITLE: Recombinant mycobacterial vaccine

APD:
19890605

BSPR:
Childhood vaccination is commonplace and generally successful in developed countries, where there is ready access to health services and multiple immunizations (e.g. immunization against multiple pathogens and serial or multiple immunizations against a single pathogen) are possible. In the developing world, vaccination is far less common and far more problematic. For example, only about 20 percent of the 100 million children born in She developing world each year are vaccinated against diphtheria, pertussis, tetanus, measles, poliomyelitis and tuberculosis. It is estimated that each year, 5 million children in the developing world die and another 5 million children are physically or mentally disabled by these diseases, which could be prevented if adequate immunization were possible. Availability of effective vaccines which can confer long-term immunity with a single administration would, of course, be valuable in both developed and developing countries.

BSPR:
Vaccination of adults is also helpful in preventing many diseases in adults and, as is the case with children, in developing countries may prove to be difficult to carry out, particularly if multiple immunizations are necessary. Diseases such as leprosy, malaria, tuberculosis, and poliomyelitis, among others, have a high incidence among adults in Africa, Asia and Latin America and are the causes of thousands of deaths annually.

BSPR:
On the other hand, Bacille Calmette-Guerin (BCG), an avirulent strain of M. bovis, is the most widely used human vaccine in the world and has been used as a live vaccine for more than 50 years. In the past 35 years, it has been administered to over 2.5 billion people, with remarkably few adverse effects (e.g., estimated mortality of 60/billion). BCG has been found in numerous studies to have protective efficacy against tuberculosis. Recently, however, it was found not to be effective in preventing pulmonary tuberculosis in Southern India. Tuberculosis Prevention Trial, Madras, Indian Journal of Medical Research, 72 (suppl.):1-74 (1980).

BSPR:
The present invention further relates to recombinant mycobacteria which express DNA of interest which has been integrated into the mycobacterial DNA or which is maintained extrachromosomally as a plasmid. Such recombinant mycobacteria can be produced by introducing DNA of interest into any appropriate mycobacterium, such as M. smegmatis, M. bovis-BCG, M. avium, M. phlei, M. fortuitum, M. lufu, M. paratuberculosis, M. habana, M. scrofulaceum and M. intracellulare. In recombinant mycobacteria in which DNA of interest is integrated into genomic DNA, the DNA of interest is present in such a manner that 1) a mycobacterial gene is replaced (i.e., is no longer present in the mycobacterial genome) or 2) the DNA of interest is inserted into a mycobacterial gene, with the result a) that the mycobacterial gene is left intact and functional or b) that the

mycobacterial gene is disrupted and rendered nonfunctional.

BSPR:
The resulting genetically recombinant mycobacteria (e.g., recombinant BCG, recombinant M. smegmatis) are particularly useful as vehicles by which the DNA of interest can be expressed. These are referred to as genetically recombinant mycobacteria or mycobacterial expression vehicles. Such vehicles can be used, for example, as vaccine vehicles which express a polypeptide or a protein of interest (or more than one polypeptide or protein), such as an antigen or antigens, for one or more pathogens of interest. The recombinant mycobacteria can also be used as a vehicle for expression of immunopotentiators, enzymes, pharmacologic agents and antitumor agents; for expression of a polypeptide or a protein useful in producing an anti-fertility vaccine vehicle; or for expression of stress proteins, which can be administered to evoke an immune response or to induce tolerance in an autoimmune disease (e.g., rheumatoid arthritis). Recombinant mycobacteria can, for example, express protein(s) or polypeptide(s) which are growth inhibitors or are cytocidal for tumor cells (e.g., interferon .alpha., .beta. or .gamma.; interleukins 1-7, tumor necrosis factor (TNF) .alpha. or .beta.) and, thus, provide the basis for a new strategy for treating certain human cancers (e.g., bladder cancer, melanomas). Pathogens of interest include any virus, microorganism, or other organism or substance (e.g., a toxin or toxoid) which causes disease. The present invention also relates to methods of vaccinating a host with the recombinant mycobacterium to elicit protective immunity in the host. The recombinant vaccine can be used to produce humoral antibody immunity, cellular immunity (including helper and cytotoxic immunity) and/or mucosal or secretory immunity. In addition, the present invention relates to use of the antigens expressed by the recombinant cultivable mycobacterium as vaccines or as diagnostic reagents.

BSPR:
BCG in particular has important advantages as a vaccine vehicle in that: 1) it is the only childhood vaccine currently given at birth; 2) in the past 40 years, it has had a very low incidence of adverse effects, when given as a vaccine against tuberculosis; and 3) it can be used repeatedly in an individual (e.g., in multiple forms).

DRPR:
FIG. 4 shows replication of phAE1 on BCG. It compares lysis of the Glaxo vaccine strain of BCG by DS6A, which is a mycobacteriophage known to plaque on M. tuberculosis and BCG, but not on other mycobacteria; phage 33D, known to plaque on M. smegmatis and not BCG; and phage TM4, which plaques on both species.

DRPR:
FIG. 9 shows results of agarose gel electrophoretic analysis of DNA from pIJ666::pAL5000 recombinant shuttle plasmids isolated from 3 independent pools of M. smegmatis transformants (lanes 1, 2, 3). Following separate transformations of each of these plasmid pools into M. coli strain x2338, unique plasmids were isolated from single purified transformants, designated pYUP13, pYUP14 and pYUP15, and are shown in lanes 5, 6, and 7, respectively. Lane 4 contains the M. fortuitum plasmid, pAL5000, and lane 8 contains the library of plJ666::pAL5000 recombinants. The size of the shuttle plasmids isolated from either M. smegmatis or E. coli is identical to the size of the recombinant library, indicating stability of the construct.

DEPR:
In order to successfully introduce DNA of interest into a mycobacterium or into the mycobacterial genome by means of the shuttle vector or plasmid vector of the present invention or by homologous recombination, the following general approaches were followed. Although it is described in terms of M. smegmatis and M. bovis-BCG, it is to be understood that it can also be used to introduce DNA of interest into other mycobacteria and that these other genetically recombinant mycobacteria can also be expression or vaccine vehicles. Such other mycobacteria include: M. smegmatis, M. bovis-BCG, M. avium, M. phlei, M. fortuitum, M. lufu, M. paratuberculosis, M. habana, M. scrofulaceum, and M. intracellulare. In the case of slow growing mycobacteria (e.g., M. bovis-BCG and M. tuberculosis) to be

used as vaccine vehicles, it is particularly valuable to go through (i.e., introduce DNA encoding an antigen or antigens of interest into) M. smegmatis and, subsequently, into M. bovis-BCG.

DEPR:
Thus, this demonstrates successful construction of E. coli-mycobacterial shuttle phasmids that are recombinant DNA molecules that not only have the ability to replicate in E. coli as plasmids and in mycobacteria as phages, but also have the ability to be packaged into bacteriophage lambda heads or into mycobacteriophage particles. It also demonstrates that recombinant DNA has been introduced into both a fast-growing mycobacterium (M. smegmatis) and a slow-growing mycobacterium (M. bovis-BCG). This makes it possible to infect BCG vaccine strains with the shuttle phasmids and, thus, to introduce cloned genes into mycobacteria. Thus, this eliminates the need to develop a transfection system for BCG. That is, because the E. coli-mycobacterial shuttle phasmid, upon transfection into mycobacteria is packaged into mycobacterial particles, DNA of interest can be introduced into slow-growing mycobacteria (e.g., BCG) by transduction, rather than transfection. Until now, this could not be done and this advance makes it possible to produce recombinant mycobacterial vaccine vehicles, which can be used to immunize against one or more antigens of interest.

DEPR:
Introduction of new genes (e.g., DNA of interest encoding antigens) into mycobacteria by means of the shuttle phasmid entails cloning DNA fragments into the shuttle phasmid in E. coli and subsequently transfecting them into M. smegmatis spheroplasts. This yields recombinant phage particles containing the cloned gene(s). Using the resulting M. smegmatis spheroplasts containing the recombinant phages, it is possible to infect BCG with high efficiency (approaching 100% efficiency), thus introducing DNA of interest included in the recombinant phages into BCG. Development of conditions for establishing lysogeny or recombination, to permit stable expression of the foreign gene(s) in mycabacterial cells, is highly desirable.

DEPR:
As a result, it is possible to produce recombinant mycobacterial vaccines which can be used to immunize individuals against, for example, leprosy, tuberculosis, malaria, diphtheria, tetanus, leishmania, salmonella, schistomiasis, measles, mumps, herpes, and influenza. Genes encoding one or more protective antigens for one or more of the disease-causing pathogens can be introduced into the mycobacterium. Of particular value is the ability to introduce genes encoding antigens of pathogens which require T-cell memory or effector function. Administration of the resulting recombinant mycobacterial vaccine to a host results in stimulation of the host's immune system to produce a protective immune response.

DEPR:
The resulting "library" is introduced into M. smegmatis using, for example, electroporation. Plaques which contain shuttle phasmids containing cloned insert DNA are selected. Subsequently, recombinant M. smegmatis can be used to infect a cultivable mycobacterium, such as BCG, with high efficiency. As a result, the antigen-encoding DNA is introduced into mycobacterial genomic DNA, where it will be expressed.

DEPR:
Transformation of this library into M. smegmatis spheroplasts has been difficult, possibly due to the problem of regenerating viable cells. DNA was therefore introduced directly into intact M. smegmatis cells by electroporation to obviate possible damage to mycobacterial cells which might result from use of protocols for producing spheroplasts. Conditions were developed for electroporation of lytic phage DNA that yielded more than 5.times.10.sup.3 pfu/ug. Electroporation of the pIJ666::pAL5000 library under these conditions into M. smegmatis yielded kanamycin- and chloramphenicol-resistance transformants. Plasmid DNA isolated from pools of M. smegmatis transformants in three separate experiments was transformed back into E. coli, selecting for

kanamycin-resistance. Although pIJ666 was inserted at different sites within the pAL5000 genome in many of the isolated E. coli transformants, all plasmids were stable in both species (FIG. 9). These methods have made it possible to transform some BCG vaccine strains with the pIJ666::pAL5000 recombinant library, with expression of kanamycin-resistance, as described in Example 9 and shown in FIG. 10. Panel A of FIG. 10 shows kanamycin-resistant BCG colonies which arose after electroporation of BCG cells with shuttle plasmid DNA; panel B shows kanamycin-resistant BCG colonies that arose after electroporation without shuttle plasmid DNA. Using a similar approach, the 65 kD M. leprae gene has been introduced into BCG, in which it was expressed, as shown by results presented in FIG. 17.

DEPR:
In one embodiment of the present invention, the 65KD gene of M. leprae has been integrated into M. smegmatis genomic DNA through use of a recombinant plasmid as represented in FIG. 13, in which Fan is the M. leprae gene.

DEPR:
The recombinant plasmid (e.g., a plasmid containing the PyrF gene into which the 65KD M. leprae gene and a Kan gene were inserted) was introduced into mycobacterial cells (M. smegmatis) using standard electroporation techniques. (See Example 11). Electroporated cells were then plated onto kanamycin-containing medium. Only kanamycin-resistant (KAN.sup.R) cells grew under these conditions; such cells had integrated into genomic DNA the KAN.sup.R gene and the M. leprae gene and were also FOA.sup.S (due to the disrupted PyrF genes from the recombinant plasmid and from the mycobacterium).

DEPR:
There are numerous uses for and advantages of the phasmid and the plasmid vectors of the present invention, as well as for the method of the present invention in which they are used. These are described below and their use in constructing vaccine vehicles is described in the following sections. As a result of the present invention, by which DNA introduced into mycobacteria has been expressed, new genetic approaches to understanding questions of disease pathogenesis are now available. Using either phage or plasmid vector systems, it should be possible to insertionally mutagenize and mark genes of pathogenic mycobacteria, either by homologous recombination or by transposon mediated insertion or deletion, with the aim of identifying specific genetic functions required for virulence and pathogenesis. For example, using these vectors and mycobacteria (e.g., M. smegmatis, M. boviso-BCG), virulence genes of M. tuberculosis or M. leprae can be identified and diagnostics (diagnostic tests) developed. By specifically deleting or replacing those genes, it may be possible to develop a more specific and effective attenuated vaccine against tuberculosis than the current M. bovis-BCG vaccine. Alternatively, as specific protective antigens for tuberculosis and leprosy are identified by study of antigens recognized by T cells from resistant individuals, it will now be possible to introduce and express them in currently existing M. bovis-BCG vaccines.

DEPR:
The vectors of the present invention can also be used to identify new drugs for the prevention or treatment of tuberculosis or leprosy. For example, it is possible that a target against which a drug should be directed is an enzyme (e.g., gyrase) produced by the causative mycobacterium. The corresponding enzyme-encoding genes in M. smegmatis can be replaced, using the subject vectors, with the M. tuberculosis or the M. leprae enzyme-encoding gene(s). This results in production of a recombinant M. smegmatis which can be used for testing to identify drugs effective against the enzymes (as well as for drugs effective against M. avium and M. intracellulare).

DEPR:
The work described also demonstrates successful construction of E. coli mycobacterial shuttle phasmids that are recombinant DNA molecules that not only have the ability to replicate in E. coli as plasmids and in mycobacteria as a phages, but also have the ability to be packaged into bacteriophage lambda heads or into mycobacteriophage particles. It further demonstrates that recombinant

DNA has been introduced into both a fast-growing mycobacterium (M. smegmatis) and a slow-growing mycobacterium (BCG). This makes it possible to infect M. bovis-BCG vaccine strains with the shuttle phasmids and, thus, to introduce cloned genes into mycobacteria. Thus, this eliminates the need to develop a transfection system for BCG. That is, because the E. coli-mycobacterial shuttle phasmid, upon transfection into mycobacteria, is packaged into mycobacterial particles, DNA of interest can be introduced stably into slow-growing mycobacteria (e.g., M. bovis-BCG) by transduction, rather than transfection. This makes it possible to produce recombinant mycobacterial vaccine vehicles, which can be used to immunize against one or more antigens of interest.

DEPR:
In a similar fashion, it is possible to construct a vaccine, using a shuttle or plasmid vector and the method of the present invention, to provide specific protection against tuberculosis. Such a vaccine is particularly attractive because of the recently reported finding, described above, that presently-used vaccines are proving to be ineffective. Genes encoding immunogenic protein antigens of the tubercle bacillus M. tuberculosis have been isolated and are described in co-pending U.S. patent application Ser. No. 07/010,007, entitled "Genes Encoding Protein Antigens of Mycobacterium Tuberculosis and Uses Therefor", by Robert N. Husson and Richard A. Young, filed Feb. 2, 1987 (now abandoned), and in the continuation-in-part application, Ser. No. 07/154.331, filed by the Express Mail procedure Feb. 10, 1988), entitled "Genes Encoding Protein Antigens of Mycobacterium Tuberculosis and Uses Therefor", by Robert N. Husson, Richard A. Young and Thomas M. Shinnick, the teachings of which are incorporated herein by reference.

DEPR:
In this case, a gene encoding an immunogenic protein antigen of M. tuberculosis is introduced into BCG by means of a shuttle or plasmid vector, as described above. It is also possible to introduce more than one M. tuberculosis gene, each encoding a protein antigen, into BCG. For example, a gene encoding immunogenic M. tuberculosis antigens of molecular weight 12 kD, 14 kD, 19 kD, 65 kD and 71 kD, or a combination of two or more of these genes, can be inserted into BCG, stably integrated into genomic DNA and expressed. The result is a vaccine which is specific for immunization against tuberculosis and which induces long-lived immunity against the bacillus.

DEPR:
It is also possible, using the method of the present invention, to construct a multipurpose or multifunctional vaccine (i.e., a single vaccine vehicle which contains and expresses DNA of interest which includes more than one gene, each gene encoding a protein antigen for a different pathogen or toxin). For example, it is possible to introduce into BCG, using the shuttle vector phasmid or the plasmid vector described, a gene encoding a protein antigen for M. leprae, a gene encoding a protein antigen for M. tuberculosis, a gene encoding a protein antigen for Leishmania, and a gene encoding a protein antigen for malaria. Administration of this multi-valent vaccine would result in stimulation of an immune response to each antigen and provide long-term protection against leprosy, tuberculosis, leishmaniasis, and malaria.

DEPR:
Shuttle phasmids were constructed from the phage L1 (ATCC #27199) in a manner similar to those constructed for the TM4 phage. Doke, S., Kumamoto Medical Journal, 34:1360-1373 (1960). All of the L1-shuttle phasmids identified have the ability to lysogenize M. smegmatis. L1 has been shown to integrate into M. smegmatis chromosomal material and to form stable lysogens. Other phage, such as L3 (ATCC #27200), a phage which remains as a plasmid (extrachromosomal) and L5 (ATCC #27201) can also be used in constructing shuttle phasmids. Results showed that these shuttle phasmids will lysogenize M. smegmatis and thus made it possible to stably integrate DNA of interest into mycobacteria for the first time. The aph gene was cloned into the unique EcoRI site of the L1-shuttle phasmid designated phAE15, as described above for the TM4-shuttle phasmids in E. coli. M. smegmatis cells (mc.sup.2 6) were overlayed on top of agar on a Dubos agar plate containing kanamycin. Dilutions of the shuttle phasmid phAE15 and

phAE19 (phAE15 with the clone aph gene) were spotted on the agar lawn. The plate was incubated 5 days at 37.degree. C. for 5 days. The colonies that grew all had been lysogenized with the L1-shuttle phasmid into which the aph gene had been cloned. The resulting shuttle phasmid, phAE19, was able to lysogenize M. smegmatis cells. The resulting lysogens expressed the cloned aph gene because they were resistant to kanamycin. Furthermore, these lysogens yielded mycobacteriophage particles that also expressed the kanamycin-resistant phenotype upon subsequent transfer and lysogenization of kanamycin-sensitive M. smegmatis cells. Transfer of these phages results in cotransduction of the lysogenic state (i.e. immunity to superinfection) and kanamycin resistance. The L1 phage, used to lysogenize M. smegmatis, does not plaque on BCG. However, variants of both L1 and the shuttle phasmid phAE19 which do form placques on BCG have been isolated. These can be tested for their ability to introduce and stably express genes of interest in BCG and M. tuberculosis by means of temperate shuttle phasmids. Thus, these phages have the ability to stably introduce DNA of interest into M. smegmatis. In addition, host range variants (e.g., phAE19) which will infect and lysogenize BCG have been isolated. This has made it possible to produce a recombinant mycobacterium, containing DNA of interest. Such recombinant mycobacteria can be used as a vaccine.

DEPR:
Plasmid pAL5000 DNA, isolated as described previously, was partially digested with MboI and linear fragments of 5 kb were isolated from an agarose gel following electrophoresis. Birnboim, H. & Doly, J. Nucleic Acid Res., 7:1513-1525 (1979). These fragments were ligated to the positive selection vector pIJ666, which contain the neo gene originating from Tn5, and the P15A origin of replication and cat gene from pACYC184, that had been cleaved with BamHI and EcoRV and transformed into E. coli. Kieser, T. and R. E. Melton, Gene, 65:83-91 (1988); Berg, D. E. et al., Proc. Natl. Acad. Sci. U.S.A., 72: 3628-3632 (1975); Chang, A. C. Y and S. N. Cohen, J. Bact., 134:1141-1156 (1978) and Chi, T. et al, J. Bact., 133:816-821 (1978). Chloramphenicol-resistant transformants (200 colonies, resistant to 25 g/ml) were pooled and grown in mixed culture, from which plasmids were isolated. Birnboim, H. and J. Doly, Nucleic Acid Res., 7:1513-1525 (1979). This library of pIJ666::pAL5000 hybrid plasmids was transformed into M. smegmatis by electroporation using the Gene Pulser (Biorad) electroporator. Chassy, B. M. and J. L. Flickinger FEMS Microbiology Letters, 44:173-177 (1987). Fresh cultures of mc.sup.2 6 cells were grown in M-ADC-TW broth with shaking to an A.sub.600 =1.7. The cells were harvested by centrifugation, washed in electroporation buffer (7 mM phosphage, pH7.2-272 mM sucrose) and resuspended to one tenth the original volume. Plasmid DNA (1 ug) was added to an electroporation cuvette containing 0.8 ml of M. smegmatis cells. Following a 10 minute incubation on ice, the cells were subjected to a single pulse of electroporation (25 uF at 6250 V/cm), then mixed with an equal volume of MoADC-TW broth and incubated at 37.degree. C. for 2 hours. The cells were then plated on 7H10 agar plates containing 10 ug/ml kanamycin and incubated for 7 days at 37.degree. C. The kanamycin-resistant transformants were subcultured in 7H9-ADC-TW both containing 10 ug/ml kanamycin and retained their ability to plaque phage D29, confirming that they were M. smegmatis. Froman, S. et al., Am. J. Public Health, 44:1326-1334 (1954). These transformants were also resistant to 100 ug/ml of chloramphenicol. Plasmid DNA was isolated from 1 ml sample of cells by a modification of the procedure of Birnboim and Doly, incubating overnight sequentially in lysozyme, alkaline-SDS and finally high-salt. The DNA isolated from M. smegmatis was transformed into 2338 and yielded more than 10.sup.4 kanamycin-resistant E. coli transformants per ug of DNA. Birnboim, H. and J. Doly, Nucleic Acids Res., 7:1513-1525 (1979). All unique plasmids isolated from individual E. coli transformants could transform and confer kanamycin- and chloramphenicol-resistance to M. smegmatis.

DEPR:
The M. leprae gene encoding stress-induced 65 kDa antigen has also been introduced and expressed in M. smegmatis and BCG. The M. leprae gene was cloned into an E. coli-Mycobacteria shuttle plasmid, designated pYUB12, which is a member of the group of shuttle plasmids, previously designated pYUP, which includes pYUP1100. The resulting construct, pYUB39, was transformed into both M. smegmatis and BCG-Pasteur and cell lysates from transformants were

electrophoresed on SDS-polyacrylamide gels. The resulting gel was blotted onto nylon membrane that was then probed with a mouse monoclonal antibody that recognizes the M. leprae-specific epitope IIE9. The blot was then probed with mouse-specific rabbit antibodies linked to alkaline phosphatase, developed for phosphatase activity, and photographed. The resulting gel demonstrates that the cloned gene encoding the foreign M. leprae 65 kDa antigen is expressed in both M. smegmatis and BCG, as represented in FIG. 17, which is a photograph of the Western blot analysis of the SDS polyacrylamide gel electrophoresis of cell lysates containing the recombinant plasmids pYUB12 or pYUB39.

DEPR:
Mycobacterial genomic DNA was partially digested with Sau3A, size selected by agarose gel electrophoresis onto DE81 paper, eluted with high salt, ethanol precipitated and ligated into pUC19 which had been cleaved with BamHI and treated with calf intestinal phosphatase. DH5alpha, made competent for transformation by the procedure of Hanahan, were transformed with this ligation and plated onto Luria Bertani agar containing 50 ug/ml ampicillin. The proportion of colonies containing recombinant plasmids was determined by plating onto indicator plates containing XGal and IPTG and determining the ratio of white colonies to total (white plus blue) colonies. Pooled plasmid DNA was obtained by scraping colonies from the plates, resuspending in 50 mM Tris pH 8.0, 10 mM EDTA, 50 mM glucose. The resulting suspension was processed by the alkaline lysis method for obtaining plasmid DNA. The M. smegmatis recombinant DNA library consists of 35,000 independent initial transformants, of which 854 were recombinant. The M. bovis-BCG recombinant DNA library consists of 64,000 independent initial transformants of which 55% were recombinant.

DEPR:
pPP25, a recombinant plasmid containing DNA from M. smegmatis able to complement pyrF E. coli, was digested with BamHI and ligated to the 1.3 kB BamHI fragment encoding aminoglycoside phosphotransferase of Tn903, isolated from pUC4kSAC. The Eco RI fragment of Y3178 containing the gene encoding the M. leprae 65 kD antigen was subsequently cloned into the unique XhoI and EcoRV sites in the mycobacterial DNA in this plasmid. In each case the transcriptional orientations of the mycobacterial open reading frame, the kanamycin resistance gene and the M. leprae 65 kD gene were determined to be in the same orientation.

DEPL:
is used to transform mycobacterial cells, such as M. smegmatis or M. bovis-BCG. The recombinant plasmid is introduced into mycobacterial cells using known techniques. In one embodiment, the plasmid is introduced by means of electroporation, using standard bacterial electroporation procedures. (See Example 11).

DEPC:
Construction of a Recombinant Plasmid for Introduction of the Kan Gene into M. smegmatis and Integration of Kan into M. smegmatis Genome

CLPR:
6. A recombinant mycobacterium of claim 5, which is Mycobacterium bovis BCG, Mycobacterium smegmatis or a genetic variant thereof.

CLPR:
8. A recombinant mycobacterium which is a recombinant Mycobacterium bovis-BCG, recombinant Mycobacterium smegmatis, or a genetic variant thereof, said recombinant mycobacterium capable of expressing DNA of interest, wherein the DNA of interest is stably integrated into the mycobacterial genomic DNA and encodes at least one protein or polypeptide of interest selected from the group consisting of: antigens, enzymes, lymphokines, immunopotentiators, and reporter molecules.

CLPR:
12. Recombinant Mycobacterium smegmatis lysogenized with shuttle phasmid phAE19, deposited at the American Type Culture Collection under Accession No. 67746.

CLPR:
14. A recombinant shuttle vector of claim 13 wherein the bacterium is selected from the group consisting of E. coli, Streptomyces, and Bacillus and the mycobacterium is Mycobacterium bovis-BCG, Mycobacterium smegmatis or a genetic variant thereof.

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L29: Entry 2 of 3 File: USPT Dec 6, 1988

DOCUMENT-IDENTIFIER: US 4789658 A
TITLE: Immunoprophylactic and immunotherapeutic agents

PRAD:
19820315

DEPR:
Mouse leukemic cells, LSTRA, were X-ray irradiated (8,000R) to remove tumorgenesity and employed as tumor vaccine, or tumor antigen. X-ray irradiated LSTRA, or its dead cells (1.times.10.sup.6 cells) was injected into food-pad of BALB/C mice. Then IL-2 (50-100 u/0.05 ml) was intravenously injected on the 5th, 7th and 9th days after vaccine injection, followed by injecting viable LSTRA cells (1.times.10.sup.6 cells) into foot-pad of these mice on the 28th day, and survival mice were observed. Survival numbers of mice in 50 days after tumor transplantation are shown in Table 9, wherein the effect of medical treatment with IL-2 in combination with tumor antigen was proved, and IL-2 was proved to have some role as adjuvant against various antigens and to be effective not only in medical treatment but also in prevention.

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End of Result Set

☐ Generate Collection

L40: Entry 2 of 2 File: USPT Dec 6, 1988

US-PAT-NO: 4789658
DOCUMENT-IDENTIFIER: US 4789658 A

TITLE: Immunoprophylactic and immunotherapeutic agents

DATE-ISSUED: December 6, 1988

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yoshimoto; Ryota	Kawasaki			JPX
Kashima; Nobukazu	Kanagawa			JPX
Hamuro; Junji	Kanagawa			JPX
Mitsugi; Koji	Kanagawa			JPX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Ajinomoto Company, Incorporated	Tokyo			JPX	03

APPL-NO: 6/ 873302
DATE FILED: June 9, 1986

PARENT-CASE:
This application is a continuation of application Ser. No. 475,180, filed Mar. 14, 1983, abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
JP	57-40369	March 15, 1982

INT-CL: [4] C12P 21/00, A61K 37/00
US-CL-ISSUED: 514/12; 514/8, 514/12, 435/68, 435/70, 530/351, 530/370, 530/371
US-CL-CURRENT: 514/2; 435/69.52, 435/70.2, 435/70.3, 435/70.4, 514/12, 514/8, 530/351, 530/370, 530/371
FIELD-OF-SEARCH: 435/68, 435/240, 435/172, 435/.3, 435/70, 435/948, 514/12, 514/2, 514/8, 424/85, 424/101, 530/351, 530/417, 530/828, 530/370, 530/371

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4350687	September 1981	Lipton et al.	424/177
☐	4359389	November 1982	Heine	210/644
☐	4368148	January 1983	Bohn	260/112B
☐	4390623	June 1983	Fabricius et al.	435/68
☐	4406830	September 1983	Fabnicius et al.	435/68
☐	4411992	October 1983	Gillis	435/68

OTHER PUBLICATIONS

Smith et al. T. Exp Med vol. 151 p. 1551, 1980 "The Functional Relationship of the Interleukins".
Itamuro et al. Immrol, vol. 3y p. 551, 1980 "Induction of Cytotoxic Penduncal Cell by 7-Cell Immune Adjuvarto of the Beta (1.fwdarw.3) Glucan-Type, Lentinunandito Analogues".
Freuhauf et al. Immunephamucology, vol. 5, pp. 65-74, 1982 "The Effect of Lentinan on Production of Interleukin by Human Monocytes".
Kashima et al (Including T. Hayami and M. Izawa) Int. T. Imminopharmacol 1982 p. 269.
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ART-UNIT: 185
PRIMARY-EXAMINER: Wiseman; Thomas G.
ASSISTANT-EXAMINER: Teskin; Robin Lyn
ATTY-AGENT-FIRM: Oblon, Fisher, Spivak, McClelland & Maier

ABSTRACT:

An immunopropylactic and immunotherapeutic agent comprising human interleukin 2 of human cellular origin is disclosed along with a method of producing the agent.

1 Claims, 9 Drawing figures

WEST

End of Result Set

☐ Generate Collection

L17: Entry 2 of 2 File: USPT Jun 29, 1999

US-PAT-NO: 5916558
DOCUMENT-IDENTIFIER: US 5916558 A

TITLE: Recombinant polypeptides and peptides, nucleic acids coding for the same and use of these polypeptides and peptides in the diagnostic of tuberculosis

DATE-ISSUED: June 29, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Content; Jean	Rhode St Genese			BEX
De Wit; Lucas	Puurs			BEX
De Bruyn; Jacqueline	Beersel			BEX
Van Vooren; Jean-Paul	St-Pieters Leeuw			BEX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
N.V. Innogenetics S.A.	Ghent			BEX	03

APPL-NO: 8/ 447430
DATE FILED: May 22, 1995

PARENT-CASE:
This application is a continuation of Ser. No. 07/690,949, now abandoned, which is a 371 filing of PCT/EP90/01593, filed Sep. 19, 1990.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	89402571	September 19, 1989

INT-CL: [6] C07K 5/00, G01N 33/53, C07H 21/04, C12Q 1/68
US-CL-ISSUED: 424/130.1; 424/187.1, 435/6, 435/7.1, 435/69.1, 435/70.1, 435/71.1, 435/172.3, 435/243, 435/325, 435/320.1, 530/300, 530/350, 536/23.1, 536/24.1, 536/24.3, 536/24.31, 536/24.32, 536/24.33
US-CL-CURRENT: 424/130.1; 424/187.1, 435/243, 435/320.1, 435/325, 435/6, 435/69.1, 435/7.1, 435/70.1, 435/71.1, 530/300 , 530/350, 536/23.1, 536/24.1, 536/24.3, 536/24.31, 536/24.32, 536/24.33
FIELD-OF-SEARCH: 435/6, 435/69.1, 435/7.1, 435/320.1, 435/172.3, 435/70.1, 435/71.1, 435/325, 435/243, 424/130.1, 424/187.1, 530/300, 530/350, 536/23.1, 536/24.1, 536/24.3-24.33, 935/77, 935/78

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4299916	November 1981	Litman et al.	435/6
☐	4683195	July 1987	Mullis et al.	435/6

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
A 905 582	April 1987	BEX	
0 288 306	October 1988	EPX	

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Wosaae et al. (1987) Inf. and Immunity, vol. 55, No. 12, pp. 2922-2927.
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H. Tasaka et al. Chemical Abstracts, vol. 99, n.degree. 11, Sep. 12, 1983, p. 413, abstract n.degree. 86251m, Columbus Ohio, US.
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H.G. Wiker et al. Int. Archs. Allergy Appl. Immun., vol. 81, 1986, pp. 307-314, S. Karger AG, Basel, DE.
M. Borremans et al. Infection and Immunity, vol. 57, n.degree. 10, Oct. 1989, pp. 3123-3130, American Society for Microbiology.
Andersen (1994) Infection and Immunity, vol. 62, No. 6, pp. 2536-2544.
De Wit et al. (1990) Nucleic Acids Research, vol. 18, No. 13, p. 3995.
Wilker et al. (1990) Infection and Immunity, vol. 58, No. 1, pp. 272-274.
De Bruyn et al. (1989) J. of Gen. Microbiology, vol. 135, pp. 79-84.

ART-UNIT: 189
PRIMARY-EXAMINER: Marschel; Ardin H.
ATTY-AGENT-FIRM: Fish & Richardson P.C.

ABSTRACT:

The invention relates to recombinant polypeptides and peptides which can also be used for the diagnosis of tuberculosis. The invention also relates to a process for preparing the above polypeptides and peptides, which are in a state of biological purity such that they can be used as part of the active principle in the preparation of vaccines against tuberculosis. The invention additionally relates to nucleic acids coding for said polypeptides and peptides.

44 Claims, 62 Drawing figures

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=> s tuberculosis(s)(32 or 32A or 32kd?)
L7         1966 TUBERCULOSIS(S)(32 OR 32A OR 32KD?)

=> s l7 and py<1998
   2 FILES SEARCHED...
L8         1388 L7 AND PY<1998

=> s tuberculosis(s)((32 or 32A)(w)kd? or 32kd?)
L9           85 TUBERCULOSIS(S)((32 OR 32A)(W) KD? OR 32KD?)

=> s l9 and py<1998
   2 FILES SEARCHED...
L10          55 L9 AND PY<1998

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PROCESSING COMPLETED FOR L10
L11          27 DUP REM L10 (28 DUPLICATES REMOVED)

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L11   ANSWER 1 OF 27  BIOTECHDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-04108  BIOTECHDS
TITLE:            Crystalline forms of InhA enzyme;
                     Mycobacterium tuberculosis recombinant
                     2-transenoyl-acyl-carrier-protein-reductase production,
                     purification and crystallization
AUTHOR:           Sacchettini J; Blanchard J; Jacobs Jr W R
PATENT ASSIGNEE:  Univ.Yeshiva; Albert-Einstein-Coll.Med.
LOCATION:         Bronx, NY, USA.
PATENT INFO:      US 5702935 30 Dec 1997
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14
24/27 27

also antigen 85-A

85 complex antigen

APPLICATION INFO: US 1994-234011 28 Apr 1994
PRIORITY INFO: US 1994-234011 28 Apr 1994
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 1998-076420 [07]
AN 1998-04108 BIOTECHDS
AB Mycobacterium **tuberculosis** InhA recombinant enzyme, NADH-dependent 2-transenoyl-acyl-carrier-protein-reductase, in crystalline form is claimed. The production of the recombinant protein and its purification are also disclosed. The InhA gene was fused to ATG of the plasmid pET expression vector, plasmid pET-15b by engineering a unique NcoI site into the inhA coding sequence. The resulting plasmid was transformed into a phage lambda lysogen containing the phage T7 polymerase fused to a lac-promoter, which is inducible by IPTG. The cells were grown at 37 deg in rich medium (2 x YT medium containing glycerol) to an optical density of 2-3. IPTG was added to a final concentration of 2 mM and induction continued for 3 hr. The cells were harvested, shel frozen and stored at -70 deg. Cells were thawed in the presence of buffer containing a mixture of protease-inhibitors, and disrupted by 2 passaged through a French press. Upon induction, about 20% of the cell protein was **32 kDa** protein; a protein absent without induction. The crystals may be studied to facilitate development of herbicides and antibiotics capable of inhibiting InhA activity. (22pp)

L11 ANSWER 2 OF 27 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97378929 MEDLINE
DOCUMENT NUMBER: 97378929 PubMed ID: 9234526
TITLE: Immunogenicity and efficacy of a tuberculosis DNA vaccine encoding the components of the secreted antigen 85 complex.
AUTHOR: Lozes E; Huygen K; Content J; Denis O; Montgomery D L; Yawman A M; Vandenbussche P; Van Vooren J P; Drowart A; Ulmer J B; Liu M A
CORPORATE SOURCE: Pasteur Institute of Brussels, Mycobacterial Immunology, Department Virology, Brussels, Belgium.
SOURCE: VACCINE, **(1997 Jun)** 15 (8) 830-3.
Journal code: X6O; 8406899. ISSN: 0264-410X.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 19971105
Entered Medline: 19971023

AB BALB/c and C57BL/6 mice were injected intramuscularly with plasmid DNA encoding the three components of the immunodominant 30-**32 kDa** antigen 85 complex (Ag85A, Ag85B, and Ag85C) from Mycobacterium **tuberculosis** culture filtrate, in order to investigate the utility of nucleic acid vaccination for induction of immune responses against mycobacterial antigens. Ag85A and Ag85B encoding plasmids induced a robust Th1-like response towards native Ag85, characterized by elevated levels of interleukin (IL)-2, interferon-gamma, and TNF-alpha. Levels of IL-4, IL-6, and IL-10 were low or undetectable. Plasmid encoding Ag85C was not effective. Cytotoxic T cell activity was also generated in in vitro restimulated splenocyte cultures from Ag85A and Ag85B DNA vaccinated mice. Finally, Ag85A and Ag85B DNA vaccination conferred significant protection against mycobacterial replication in

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M59

L37: Entry 6 of 6 File: USPT Jun 8, 1993

DOCUMENT-IDENTIFIER: US 5217898 A
TITLE: Expression of the P. falciparum transmission-blocking antigen in yeast

APD:
19910508

ABPL:
The present invention relates to transmission-blocking vaccines against malaria. Vaccines of the present invention contain a recombinant Pfs25 Plasmodium falciparum protein produced by yeast cells and to yeast cells producing the protein. Mice and monkeys inoculated with the yeast-expressed Pfs25 of the present invention have developed antibodies with transmission-blocking activity. The present invention also relates to methods of preventing or treating malarial infections using the vaccines of the present invention.

BSPR:
The present invention relates to transmission-blocking vaccines against malaria and methods of preventing the transmission of the disease.

BSPR:
Malaria vaccines are being developed against different stages in the parasite's life-cycle including the sporozoite, asexual erythrocyte, and sexual stage. Each development increases the opportunity to control malaria in the many diverse settings within which the disease occurs. Sporozoite vaccines would prevent mosquito-induced infections. First generation vaccines of this type have been tested in humans. Asexual erythrocytic stage vaccines would be useful in reducing the severity of the disease. Multiple candidate antigens have been cloned and tested in animals and in humans.

BSPR:
One type of vaccine being investigated to slow or reverse the worsening epidemic of malaria is a transmission-blocking vaccine [Miller et al., Science 234:1349 (1988)]. Transmission of Plasmodium falciparum from host to mosquito vector can be blocked by monoclonal antibodies against a 25 kDa sexual stage surface protein, Pfs25, expressed on zygotes and ookinetes [Vermeulen et al., J. Exp. Med. 162:1460 (1985)]. The gene encoding Pfs25 has been cloned [Kaslow et al., Nature 333:74 (1988)], and the deduced amino acid sequence revealed a striking feature, the presence of four tandem epidermal growth factor (EGF)-like domains. EGF-like domains are cysteine rich and depend on proper disulfide bond formation for structural integrity [Savage et al., J. Biol. Chem. 247:7612 (1972)]. Of the monoclonal antibodies previously known to block transmission, none recognize the reduced Pfs25 antigen [Vermeulen et al., J. Exp. Med. 162:1460 (1985) and Carter et al., Prog. Allergy 41:193 (1988)], suggesting that for at least some of the blocking epitopes, disulfide bonds are involved in creating proper conformation.

BSPR:
Before Pfs25 can be used as an effective transmission-blocking vaccine, peptides or recombinant DNA-derived Pfs25 molecules having the appropriate conformation for immunological activity in vivo must be produced in large quantities. In addition, adjuvant formulations must be developed which are suitable for use in human transmission-blocking vaccines.

BSPR:
It is another object of the present invention to provide a transmission-blocking vaccine.

DRPR:
FIG. 2 shows antibody titres of Aotus monkeys immunized with Pfs25-B and MTP-MF59 adjuvant. Monkeys were injected intramuscularly at four weekly intervals (.dwnarw.).

DEPR:
The present invention relates to transmission-blocking vaccines against malaria. From these studies, it was determined that yeast-produced Pfs25 elicits the production of transmission-blocking antibodies. The present inventors have engineered, by chemical synthesis and mutagenesis, a gene and expressed same in yeast cells to produce an analogue of Pfs25, designated Pfs25-B. Absent from the yeast-expressed protein was the amino-terminal secretory sequence and the hydrophobic carboxyl terminal region. The N-linked glycosylation sites were also removed from Pfs25-B. Pfs25-B was shown to react with conformation dependent monoclonal antibodies despite its conformational changes. In addition, Pfs25-B elicited transmission-blocking activity in mice and monkeys.

DEPR:
The present invention further relates to transmission-blocking vaccines against malaria. A transmission-blocking vaccine prevents the transmission of Plasmodium falciparum from host to mosquito vector. The present invention provides a yeast-produced protein which elicits transmission-blocking antibodies in both mice and monkeys.

DEPR:
Transmission-blocking vaccines of the present invention comprise the yeast-expressed Pfs25 protein or analogue thereof present in an amount sufficient to induce immunization against malaria. The vaccine can further comprise an adjuvant, such as, for example, MTP-MF59 or alum. The vaccine can be administered via intradermal, subcutaneous, intramuscular, nasopharyngeal or respiratory routes, for example, inhalation.

DEPR:
The transmission-blocking vaccines of the present invention can also include other malarial antigens. For example, the transmission-blocking vaccine of the present invention include antigens generating protective malarial immunity.

DEPR:
The present invention also relates to methods of preventing transmission of malarial infections. Methods of the present invention comprise administering to a patient a vaccine of the present invention in an amount sufficient to induce transmission-blocking activity. The treatment consists of a single administration or a series of administrations. When given as a series administrations, inoculations subsequent to the initial administration are given to boost the immune response and may be referred to as booster inoculations.

DEPR:
The treatment given will vary in the number of inoculations and the vaccine used depending on several factors, such as the patient's conditions and the route of administration. These factors are easily assessed by the physician and an appropriate treatment determined therefrom.

DEPR:
The purified protein was used to immunize mice (Swiss-Webster) and Aotus trivirgatus monkeys together with the muramyl tripeptide (MTP) adjuvant MF59. The MF59 adjuvant has been used previously to elicit high antibody titres in rodents and goats with other recombinant malaria proteins. MF59 has also been demonstrated to be safe and efficacious in humans when used in conjunction with a yeast-derived human immunodeficiency virus-1 (HIV-1) envelope protein [Abrignani et al., Proc. Natl. Acad. Sci. U.S.A. 87:6136 (1990)].

DEPR:
Mice were immunized with Freunds adjuvant plus Pfs25-B or MF59 plus Pfs25-B. In the Freunds adjuvant group, mice were immunized three times at three weekly intervals with 50 ug of Pfs25-B in a final volume of 100 .mu.l as described previously. In the MF59 adjuvant groups, mice were immunized, using the same protocol with Pfs25-B, falc 2.3, hEGF or hSOD (50 ug per injection). Animals were bled one week after the final immunization and antibody titres were measured in the ELISA format as described previously [see Table 7 below].

DEPR:
Monkeys were injected intramuscularly with three 100 .mu.g doses of Pfs25-B in MF59 at four weekly intervals (see FIG. 2). Titres were measured by ELISA every two weeks and sera taken at weeks 0, 12 and 22 were used for mosquito feeding experiments described below.

DEPR:
Humoral immune responses elicited in mice with both Freunds adjuvant and MF59 (see Table 1 below) were measured by ELISA. Also shown in Table 1 are the reactivities of antisera raised with recombinant Pfs25 against various control recombinant proteins from yeast. These include, human superoxide dismutase (hSOD) [Hallewell et al., Biotechnology 5:363 (1987)], a circumsporozoite (CS) protein from P. falciparum (falc 2.3), and human EGF [Brake et al., Proc. Natl. Acad. Sci. U.S.A. 81:4642 (1984) and George-Nascimento et al., Biochemistry 27:797 (1988)].

DEPR:
Similarly, sera from two A. trivirgatus monkeys were capable of blocking completely the development of oocysts in mosquitoes after immunization with Pfs25-B. The ability of the sera to block oocyst development was measured as above. Prebleed sera from each monkey (numbers A108 and A142) were used as controls. Transmission-blocking activities were measured at 12 and 22 weeks. Mabs 1D2 and 4B7 were also shown to block oocyst appearance at a 1:2 dilution, whereas sera from the two monkeys that were injected with MF59 alone failed to inhibit oocyst development at any of the bleeds assayed. This transmission-blocking activity persisted for nearly 4 months in one monkey and more than 6 months in the other (see Table 2B below).

DEPR:
MAB 4B7 was a product of a fusion of spleen cells from a BALB/c mouse immunized twice with recombinant vaccinia virus that were expressing Pfs25 and boosted with whole P. falciparum gametes. Supernatants from the fusion were screened for specificity to Pfs25 by immunoblot of reduced Pfs25-B. Antisera P7 was produced from mice immunized with synthetic peptides derived from the deduced amino acid sequences of Pfs25 [Kaslow et al., Nature 333:74-76 (1988)].

DEPR:
Antibodies that recognize reduced Pfs25, such as Mab 4B7, were shown to block transmission (see Table 2), suggesting that epitopes that are not dependent on disulfide bonds for conformation may elicit transmission-blocking antibodies. Despite this, however, the yeast-derived Pfs25-B of the present invention was fully capable of inducing transmission-blocking immunity in both mice and monkeys. In addition, transmission-blocking antisera did not recognize recombinant hEGF in an ELISA assay (see Table 1), nor did antisera to hEGF recognize Pfs25-B in such an assay (see Table 1). The cross-reactivity of antisera to hEGF with Pfs25-B was also below the limit of detection. The homology of Pfs25 to EGF might give rise to an auto-immune response in individuals immunized with Pfs25. Dara, however, indicates that this is not likely to be the case. It is anticipated that this lack of cross-reactivity will be similar for other members of the polypeptide family that contain EGF-like motifs and are, therefore, not likely to be a concern in transmission-blocking vaccination studies with Pfs25.

DEPR:
Several recombinant DNA-derived antigens or synthetic peptides of malaria

parasites have been shown to be only weakly immunogenic in humans [Herrington et al., Nature 328:257-259 (1987) and Gordon et al., Am. J. Trop. Med. and Hyg. 42:527-531 (1990)]. Since pfs25 is not expressed at the gametocyte stage, but appears only during sexual development in the mosquito, and has, therefore, not been subjected to immune pressure in the human host, it is anticipated that the immunogenicity of Pfs25-B in humans will closely parallel that observed in experimental animals. Furthermore, transmission-blocking immunity elicited in both mice and monkeys was observed with MTP-MF59, an adjuvant that has been shown previously to be safe and efficacious in humans [Abrignani et al., Proc. Natl. Acad. Sci. U.S.A. 87:6136-6140 (1990)]. Based on the extremely high yields of the Pfs25 protein that can be obtained from yeast, together with the immunogenicity data, the combination of Pfs25 from yeast and MTP-MF59 represents an excellent initial formulation for the study of transmission-blocking immunity in humans.

DETL:
TABLE 1 _____ Antibody titres developed in mice by immunization with re- combinant Pfs25-B and either Freunds (FCA/FIA) or MF59 adjuvants. Assay Protein Antigen Adjuvant Pfs 25B Falc 2.3 hEGF hSOD
_____ Pfs25-B FCA/FIA 42,000 <100 <100 <100 Pfs25-B MF59 31,625 <100 <100 <100 Falc 2.3 MF59 <100 20,200 <100 ND hEGF MF59 <100 <100 9,100 ND hOSD MF59 <100 ND <100 18,750
_____ ND = Not determined

DETL:
TABLE 2 _____ Inhibition of oocyst development by sera from immunized animals. Infect- Mean Oocyst ivity Sample Numbers (Range) % of Control ##STR1## _____ Pooled Preimmune B 100% 16/16 (1-22) Pfs25-B (CFA/IFA) 0 <1% 1/19 (0-1) Pfs25-B (MF59) 0 0% 0/18 (0) Falc 2.3 (MF59) 4 50% 17/18 (0-13) Mab 1D3 0 0% 0/16 (0) B A108 Preimmune 39 100% 20/21 (0-89) A142 Preimmune 25 100% 21/21 (5-75) A108 Week 12 0 <1% 1/24 (0-1) A142 Week 12 0 0% 0/20 (0) A108 Week 22 0 0% 0/28 (0) A142 Week 22 2.6 10% 15/26 (0-35) Mab 1D2 0 <1% 1/20 (0-1) Mab 4B7 0 0% 0/24 (0)
_____

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End of Result Set

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L37: Entry 6 of 6 File: USPT Jun 8, 1993

US-PAT-NO: 5217898
DOCUMENT-IDENTIFIER: US 5217898 A

TITLE: Expression of the P. falciparum transmission-blocking antigen in yeast

DATE-ISSUED: June 8, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kaslow; David C.	Kensington	MD		
Barr; Philip J.	Oakland	CA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The United States of America as represented by the Secretary of Health and Human Services	Bethesda	MD			06
Chiron Corporation	Emeryville	CA			02

APPL-NO: 7/ 697275
DATE FILED: May 8, 1991

PARENT-CASE:
The present application is a continuation-in-part application of the Kaslow et al application Ser. No. 07/658,845 filed Feb. 22, 1991, abandoned, which is a continuation-in-part application of Miller et al application, Ser. No. 07/188,918 filed May 2, 1988, abandoned. The entire contents of both applications are hereby incorporated by reference.

INT-CL: [5] C12P 21/02, C12P 19/34, C12N 15/00, C12N 7/00
US-CL-ISSUED: 435/255; 435/69.1, 435/69.3, 435/91, 435/172.3, 435/235.1, 435/320.1, 435/256, 536/23.7, 530/350, 935/10 , 935/28, 935/37, 935/56, 935/65, 935/69
US-CL-CURRENT: 435/254.2; 435/235.1, 435/320.1, 435/69.1, 435/69.3, 530/350, 536/23.7
FIELD-OF-SEARCH: 435/69.1, 435/69.3, 435/91, 435/172.3, 435/235.1, 435/320.1, 435/255, 435/256, 536/27, 530/350, 935/10, 935/28, 935/37, 935/56, 935/65, 935/69

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4546082	October 1985	Kurjan et al.	435/68

OTHER PUBLICATIONS

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Barr et al, J. Biol. Chem, vol. 263, pp. 16471-16478, (1988).
Gibson, H. L., et al., "Expression in Yeast of Pfs25, A Sexual Stage Antigen of Plasmodium falciparum", The 38th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Honolulu, Hawaii, Dec. 10-14, 1989.

ART-UNIT: 183
PRIMARY-EXAMINER: Ellis; Joan
ABSTRACT:

The present invention relates to transmission-blocking vaccines against malaria. Vaccines of the present invention contain a recombinant Pfs25 Plasmodium falciparum protein produced by yeast cells and to yeast cells producing the protein. Mice and monkeys inoculated with the yeast-expressed Pfs25 of the present invention have developed antibodies with transmission-blocking activity. The present invention also relates to methods of preventing or treating malarial infections using the vaccines of the present invention.

5 Claims, 3 Drawing figures

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L29: Entry 1 of 3 File: USPT May 23, 1995

DOCUMENT-IDENTIFIER: US 5417970 A
TITLE: Drugs containing a glycosylated interleukin-2

PRAD:
19881021

PRAD:
19881021

BSPV:
Vaccination (using IL-2 as an adjuvant).

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L40: Entry 1 of 2 File: USPT May 23, 1995

US-PAT-NO: 5417970
DOCUMENT-IDENTIFIER: US 5417970 A

TITLE: Drugs containing a glycosylated interleukin-2

DATE-ISSUED: May 23, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Roskam, deceased; Willem	late of Montgiscard			FRX
Basuyaux; Bertrand	Courbevoie			FRX
Ferrara; Pascual	Villefranche de Lauragais			FRX
Laporte; Martine	Ramonville Saint-Agne			FRX
Maureaud; Thierry	Auzielle			FRX
Vita; Natalio	Toulouse			FRX
Bayol; Alain	Tournefeuille			FRX
Perry; Genevieve	Toulouse			FRX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Sanofi	Paris			FRX	03

APPL-NO: 8/ 152886
DATE FILED: November 16, 1993

PARENT-CASE:
This application is a continuation of application Ser. No. 07/715,862, filed Jun. 17, 1991, which in turn is a continuation of Ser. No. 07/499,472, filed on Jun. 21, 1990, both now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	88 13865	October 21, 1988
FR	89 05150	October 21, 1988

INT-CL: [6] A61K 37/02, C07K 3/20, C07K 3/22, C07K 15/14
US-CL-ISSUED: 424/85.2; 435/69.52, 530/351, 530/416, 530/417
US-CL-CURRENT: 424/85.2; 435/69.52, 530/351, 530/416, 530/417
FIELD-OF-SEARCH: 530/351, 530/412, 530/416, 530/417, 435/69.12, 435/71.1, 435/72.85, 424/85.2, 514/12, 514/801

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	3024167	March 1962	Damaskus	514/801
☐	4490289	December 1984	Stern	530/351
☐	4675383	June 1987	Bohlen et al.	520/351
☐	4778879	October 1988	Mertelsmann et al.	530/351
☐	5217881	June 1993	Park	436/546

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0158487	October 1985	EPX	
0172619	February 1986	EPX	
0307285	March 1989	EPX	
WO88/00967	February 1988	WOX	

OTHER PUBLICATIONS

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ART-UNIT: 185
PRIMARY-EXAMINER: Russel; Jeffrey E.
ATTY-AGENT-FIRM: Foley & Lardner

ABSTRACT:

An interleukin-2 preparation suitable for pharmaceutical purposes, consisting essentially of disialilated glycosylated interleukin-2, monosialilated glycosylated interleukin-2, or a mixture thereof, and substantially free of organic solvents, is isolated from recombinant CHO cells transformed with a vector containing a DNA sequence coding for a natural precursor of human interleukin-2, and is purified by a multi-step process.

25 Claims, 9 Drawing figures

WEST

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L38: Entry 1 of 1 File: USPT Jul 19, 1994

US-PAT-NO: 5330754
DOCUMENT-IDENTIFIER: US 5330754 A

TITLE: Membrane-associated immunogens of mycobacteria

DATE-ISSUED: July 19, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kapoor; Archana	75014 Paris			FRX
Munshi; Anil	LaJolla	CA	92092-0573	

APPL-NO: 7/ 906395
DATE FILED: June 29, 1992

INT-CL: [5] C07K 13/00, C07K 15/04, A61K 39/04
US-CL-ISSUED: 424/190.1; 530/350, 435/69.3, 435/195, 514/2, 536/23.7, 424/248.1
US-CL-CURRENT: 424/190.1; 424/248.1, 435/195, 435/69.3, 514/2, 530/350, 536/23.7

FIELD-OF-SEARCH: 435/69.3, 435/69.7, 435/252.3, 435/253.1, 530/324, 530/350, 424/92, 424/93

PRIOR-ART-DISCLOSED:

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L11 ANSWER 27 OF 27 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 86291713 MEDLINE
DOCUMENT NUMBER: 86291713 PubMed ID: 2426875
TITLE: The patterns of complex and partially purified mycobacterial antigens in macrophage migration inhibition testing.
AUTHOR: Kubin M; Wisingerova E; Pekarek J; Prochazka B
SOURCE: ZENTRALBLATT FUR BAKTERIOLOGIE, MIKROBIOLOGIE, UND HYGIENE.
SERIES A, MEDICAL MICROBIOLOGY, INFECTIOUS DISEASES, VIROLOGY, PARASITOLOGY, **(1986 May)** 261 (3) 362-9.
Journal code: Y55; 8403032. ISSN: 0176-6724.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198609
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19990129
Entered Medline: 19860918

AB In rabbits immunized intratarsally by M. **tuberculosis**, M. kansasii and M. avium the responses to homologous and heterologous antigens were assessed by direct and indirect macrophage migration inhibition tests. Complex cytoplasmic antigens were obtained by disruption of bacterial mass and by ultracentrifugation of the supernatants. The partially purified antigens were prepared by gel chromatography of the complex antigens on a Sephadex G 150 column. The middle fraction (260/280 ratio approx. 1, molecular weight approx. **32 KD**) was employed as partially purified antigen. In the direct tests the migration activity of immune spleen macrophages was significantly reduced by homologous complex and partially purified antigens (MI = 0.63 to 0.72) and it differed significantly from responses obtained with heterologous antigens (MI = 0.75 to 0.92); however, these were still lower than those in nonimmunized control animals where MI ranged from 0.89 to 1.01. In the indirect tests, the strongest responses were recorded again with homologous complex and partially purified antigens (MI = 0.43 to 0.53). The responses in heterologous systems differed even more markedly than in direct tests (MI = 0.65 to 0.81); and, these were again still significantly lower than in control animals (MI = 0.89 to 0.98). In both direct and indirect tests, the complex and partially purified antigens did not vary substantially in their immunogenic capacity. The presence of cross-reacting responses in heterologous systems can be explained by a close relatedness of mycobacteria used in the immunization schedule and by the presence of common epitopes in complex and purified testing antigens.

L11 ANSWER 26 OF 27 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 88126912 MEDLINE
DOCUMENT NUMBER: 88126912 PubMed ID: 3124263
TITLE: Specific lymphoproliferation, gamma interferon production, and serum immunoglobulin G directed against a purified **32 kDa** mycobacterial protein antigen (P32) in patients with active **tuberculosis**.
AUTHOR: Huygen K; Van Vooren J P; Turneer M; Bosmans R; Dierckx P; De Bruyn J
CORPORATE SOURCE: Instituut Pasteur van Brabant, Brussels, Belgium.
SOURCE: SCANDINAVIAN JOURNAL OF IMMUNOLOGY, **(1988 Feb)** 27 (2) 187-94.
Journal code: UCW; 0323767. ISSN: 0300-9475.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198803
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880318

AB Twenty-one patients treated for active **tuberculosis** were examined for immune reactivity to purified protein derivative (PPD) and to a purified **32-kDa** protein antigen (P32) from Mycobacterium bovis, strain BCG. Lymphoproliferation of peripheral blood leucocytes to PPD and P32 was positive in 95% and 71% of the patients respectively. A positive IFN-gamma response was detected in 62% against PPD and in 48% against P32. Low blastogenesis and IFN-gamma production were observed, especially in patients with poor general health and advanced tuberculous lesions. Twelve out of twelve (100%) of the tuberculin-positive healthy volunteers responded to PPD and P32 with mean lymphoproliferation and IFN-gamma values that were higher than in the patient group. Twelve tuberculin-negative control subjects were completely unreactive to PPD and P32 antigen. On the other hand, IgG antibodies in the serum were detected in 95% of the patients against PPD, in 77% of the patients against P32 but in none of the tuberculin-positive or negative healthy volunteers. The highest IgG levels against PPD were found in those patients with the lowest in vitro lymphoproliferation and IFN-gamma production (r = -0.54; P less than 0.05). Nonspecific interferon production following induction with Newcastle disease virus, Corynebacterium parvum, or phytohaemagglutinin was comparable in the control and patient groups. Finally, low IFN-alpha titres were detected in the serum of about 50% of the patients.

L11 ANSWER 27 OF 27 MEDLINE DUPLICATE 17

WEST

End of Result Set

☐ Generate Collection

L24: Entry 8 of 8 File: USPT Jul 17, 1984

DOCUMENT-IDENTIFIER: US 4460575 A
TITLE: Vaccinal complex containing a specific antigen and vaccine containing it

BSPV:
Mycobacterium (tuberculosis, Smegmatis).

DEPR:
The bacterial biomass of Streptococcus pneumoniae I which is used for the preparation of ribosomal RNA and the capsular PS is obtained by a conventional industrial fermentation process. The only characteristic of the fermentations intended for the preparation of the ribosomal RNA is in the centrifugation of the cultures when they are in the full phase of exponential growth and at low temperature, in order to retain a maximum activity of ribosomal synthesis in the cells.

280

WEST

End of Result Set

☐ Generate Collection

L24: Entry 8 of 8 File: USPT Jul 17, 1984

US-PAT-NO: 4460575
DOCUMENT-IDENTIFIER: US 4460575 A

TITLE: Vaccinal complex containing a specific antigen and vaccine containing it

DATE-ISSUED: July 17, 1984

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
d'Hinterland; Lucien D.	Castres			FRX
Normier; Gerard	Castres			FRX
Pinel; Anne-Marie	Castres			FRX
Durand; Jacques	Castres			FRX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Pierre Fabre S.A.				FRX	03

APPL-NO: 6/ 236534
DATE FILED: February 20, 1981

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	80 03707	February 20, 1980

INT-CL: [3] A61K 39/02, A61K 39/09, C07C 103/52, C07H 21/02
US-CL-ISSUED: 424/92; 424/88, 424/180, 424/177, 536/27, 260/112R
US-CL-CURRENT: 424/197.11; 424/234.1, 424/243.1, 424/244.1, 424/245.1, 424/248.1, 424/250.1, 424/256.1, 424/257.1, 424/258.1, 424/259.1, 424/831, 530/405, 530/807, 536/23.1, 536/24.2
FIELD-OF-SEARCH: 424/92, 424/88, 536/22, 536/27, 536/28, 536/29, 260/112R

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	3725545	April 1973	Maes	424/88
☐	3952097	April 1976	Levy	536/22
☐	4285930	August 1981	Likhite	424/92

OTHER PUBLICATIONS

Chemical Abstracts, vol. 87, p. 376, Abst. No. 11603w, 1977.

ART-UNIT: 123
PRIMARY-EXAMINER: Hazel; Blondel
ATTY-AGENT-FIRM: Maky, Renner, Otto & Boisselle

ABSTRACT:

The present invention relates to a vaccinal complex containing a specific antigen. This is a vaccinal complex characterized in that it is composed of bacterial ribosomal RNA or fragments of bacterial ribosomal RNA on which are coupled from 1 to 5% by weight of a specific antigen of bacterial serotype. This complex may be used as a vaccine.

14 Claims, 0 Drawing figures